Management of Irritable Bowel Syndrome With Constipation in Adult Women

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Introduction

Irritable bowel syndrome (IBS) is a multisymptomatic disorder characterized by abdominal pain associated with altered bowel habits. According to the Rome III diagnostic criteria, IBS consists of recurrent abdominal pain or discomfort that is associated with 2 or more of the following characteristics: improvement with defecation, onset associated with a change in stool frequency, or onset associated with a change in stool form. Symptoms must have occurred at least 3 or more days per month in the last 3 months with symptom onset ≥6 months prior to diagnosis. In this article, we will discuss means of enhancing management of constipation-predominant IBS (IBS-C) in adult women, including improvement of the clinician–patient relationship, as well as treatment with an FDA-approved option for management of IBS-C. Global symptoms include “abdominal discomfort/pain,” “bowel habits,” and “other IBS symptoms.”

IBS-C is one of 3 subtypes of IBS designated by the Rome III criteria for Functional Bowel Disorders and is defined as IBS plus the occurrence of hard or lumpy stools in ≥25% of bowel movements and loose or watery stools in <25% of bowel movements in the absence of the use of antidiarrheals or laxatives (Figure 1). In addition to the symptoms of abdominal pain and altered bowel habits, more than 60% of patients may also present with non-GI symptoms. According to one community survey, 4.3% of the US population is diagnosed with IBS-C, while 15% of individuals have IBS-C without being formally diagnosed.

Recognition of IBS-C

In the absence of an identified biologic marker for IBS-C, diagnostic assessment relies on recognition of the symptoms of abdominal pain, bowel habits, and stool form and their timing in relation to each other. The American Gastroenterological Association recommends a thorough history and physical examination, identifying patients with symptoms outlined in the Rome III Criteria, and then ruling out other potential causes of the symptoms. Patients should be screened for alarm signs such as anemia, weight loss, and a family history of colon cancer, inflammatory bowel disease, or celiac disease, as any of these may indicate the presence of other disease states. In addition to the history and physical examination, asking the patient to maintain a symptom diary may aid in the diagnosis of IBS-C. In the absence of alarm signs and symptoms, constipation is a prominent and defining feature of IBS-C, and it may be challenging to differentiate between IBS-C and chronic constipation (CC). The characteristics of the 2 conditions are somewhat similar, with symptoms varying in intensity along a spectrum of abdominal pain/discomfort and stool frequency. Abdominal pain is the primary differentiating factor, being more pronounced in IBS-C than in CC. Frequency of bowel movements is more likely to be reduced in patients with CC than in patients with IBS-C, whereas Rome III defines IBS-C by stool form rather than reduced frequency.

The Importance of the Clinician–Patient Relationship

With symptom-defined conditions such as IBS-C, the importance of an effective clinician–patient relationship cannot be overstated. A patient-centered model of communication engages the patient in open-ended dialogue and includes him or her in a collaborative process regarding disease management. Reviews of literature on patient-centered communication have found this model may help improve patient outcomes, including patient satisfaction, adherence to treatment, and patient health. The patient-centered model is also associated with increased efficiency of care in terms of fewer diagnostic tests and referrals. Thus, it is recommended that such an approach be adopted when interacting with patients, especially those who may suffer from functional bowel disorders such as IBS-C.

Rome III Diagnostic Criteria for IBS-C

- Recurrent abdominal pain or discomfort associated with ≥2 of the following:
  - Improvement with defecation
  - Onset associated with a change in stool frequency
  - Onset associated with a change in stool form (appearance)
- Symptoms occurring ≥3 days per month in the last 3 months; symptom onset ≥6 months prior to diagnosis
- Hard or lumpy stools in ≥25% of bowel movements
- Loose or watery stools in <25% of bowel movements

Figure 1. Rome III diagnostic criteria for IBS-C.

Adapted from Longstreth GW, et al.
Developing this collaborative relationship may be complicated, given that patients do not always describe their symptoms clearly and effectively. Consequently, it can be helpful if the clinician not only listens closely during the patient history, but also encourages discussion. This may involve asking specific questions about what led the patient to seek treatment at this particular point, how the symptoms are affecting the patient’s ability to function, and participate in daily activities, and what expectations the patient has from the clinician.10

At a minimum, it is recommended that the clinician acknowledge the patient’s pain, provide empathy, and educate the patient about the condition, including possible triggers and available treatment options, in order to determine an appropriate treatment approach for his or her symptoms. Education about the condition should be provided in a manner that allows patients to assertively discuss their symptoms and related issues with their clinician. The patient experience is likely to be significantly improved if the patient is included in the discussion of available treatment options and establishment of realistic therapeutic goals. Furthermore, a long-term relationship with appropriate follow-up care is recommended.10

**Treatment Options for IBS-C**

IBS-C is considered difficult to treat because of its multiple triggers, variable clinical course, and the unpredictable nature and severity of its symptoms.12 In addition, the number of therapies available to manage the condition is limited.

Traditionally, treatment has included a combination of diet and lifestyle modifications, pharmacologic agents, and other therapeutic interventions to address the multitude of symptoms. Efficacy among these treatments varies widely, and although many of these remedies are currently used in clinical practice to treat IBS-C, they are not approved by the Food and Drug Administration (FDA) for the treatment of IBS-C.

A systematic review on the management of IBS was recently published by the American College of Gastroenterology Task Force on IBS.7 Therapies that are frequently used for management of patients with IBS-C were evaluated based on available published clinical evidence. Evidence levels were graded according to the strength of the recommendation and the quality of evidence: strong and weak recommendations are indicated with a 1 or 2, respectively, and high, moderate, or low quality of evidence is indicated by an A, B, or C, respectively. Some examples of the treatment ratings are 5-HT₄ receptor agonists (Grade 1A); selective C-2 chloride channel activators/AMITIZA® (lubiprostone) (Grade 1B); psychological therapies (Grade 1C); and diet, fiber, bulking agents, laxatives, antispasmodics, peppermint oil, and probiotic therapy (Grade 2C). AMITIZA, a selective type 2 chloride channel activator, is currently the only widely available FDA-approved option for treatment of IBS-C in women age 18 years of age and older. AMITIZA was found to be more effective than placebo and received a 1B rating, which is a strong recommendation with moderate evidence in the systematic review.

**AMITIZA for Treatment of IBS-C in Adult Women**

AMITIZA is a selective chloride channel activator approved by the FDA for treatment of IBS-C in women ≥18 years of age at a dose of 8 mcg twice daily taken with food and water.2 AMITIZA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction. Patients with symptoms suggestive of mechanical gastrointestinal obstruction should be evaluated prior to initiating AMITIZA therapy.

The mechanism of action of AMITIZA in the treatment of IBS-C is not fully understood, but a relationship between chloride channel activation and restoration of tight junctions of gastrointestinal epithelial cells has been hypothesized based on animal studies. AMITIZA selectively activates type 2 chloride channels, leading to the secretion of chloride into the intestinal lumen, which is followed by sodium ions and water.2,13 Tight junctions between cells act as gatekeepers for solutes and macromolecules passing between the apical and basolateral regions of the gut.14 Damaged or compromised tight junctions are associated with leakage of luminal contents through the mucosal barrier.14,15

Activation of type 2 chloride channels by AMITIZA has been shown to stimulate recovery of mucosal barrier function via the restoration of tight junction protein complexes in an isolated ischemic porcine intestine model.2,14 It is important to note, however, that the role of tight junctions in IBS-C is unclear at this time.

**AMITIZA Clinical Trials**

In a multicenter, double-blind, placebo-controlled Phase II dose-ranging study, 195 patients with IBS-C were randomized to receive placebo, AMITIZA 8 mcg twice daily, AMITIZA 16 mcg twice daily, or AMITIZA 24 mcg twice daily.16 Levels of improvement in the primary end point of abdominal pain/discomfort were similar across treatment groups, but a dose–response effect was noted with regard to the incidence of adverse events (AEs). The dose of 8 mcg, twice daily was therefore determined to offer the best combination of
tolerability and efficacy.

Two multicenter, double-blind, randomized, controlled Phase III trials were conducted to evaluate the efficacy and safety of AMITIZA 8 mcg twice daily for the treatment of IBS-C.2,17 The studies had a total intent-to-treat population of 1154 men and women aged ≥ 18 years who fulfilled modified Rome II criteria for IBS-C. IBS was defined as abdominal pain or discomfort occurring over at least 6 months with 2 or more of the following: 1) relieved with defecation; 2) onset associated with a change in stool frequency; and 3) onset associated with a change in stool form. Patients were subtyped as having IBS-C if they also experienced 2 or 3 of the following: 1) <3 spontaneous bowel movements per week, 2) >25% hard stools, and 3) >25% spontaneous bowel movements associated with straining. After a 4-week baseline/washout period, patients were randomized to receive placebo or AMITIZA 8 mcg twice daily for 12 weeks.

The two Phase III controlled trials comprised 97 (8.4%) male patients, which is insufficient to determine whether men with IBS-C respond differently to AMITIZA than women.2 For this reason, AMITIZA is indicated for adult women with IBS-C. The safety of AMITIZA in pregnancy has not been evaluated in humans. AMITIZA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women who could become pregnant should have a negative pregnancy test prior to beginning therapy with AMITIZA and should be capable of complying with effective contraceptive measures.

The primary efficacy end point was assessed weekly via electronic diaries based on patient response to a global symptom relief question.2 Subjects were asked, “How would you rate your relief of IBS symptoms (abdominal discomfort/pain, bowel habits, and other IBS symptoms) over the past week compared to how you felt before you entered the study?” and responded based on a 7-point balanced scale from “significantly worse” to “significantly better.”2,17 The primary efficacy analysis in the Phase III trials compared the proportion of “overall responders” in each arm. To be considered an overall responder, subjects were required to meet the criteria for being designated a monthly responder in at least 2 of the 3 months while on study. Monthly responder was defined as a patient who had reported “significantly relieved” for at least 2 weeks of the month or at least “moderately relieved” in all 4 weeks of that month. Patients were considered nonresponders for the monthly evaluation period if they reported “moderately worse” or “significantly worse” relief, reported an increased use of rescue medication, or if they discontinued due to a lack of efficacy.

Figure 2 represents the overall responder rates in the two Phase III trials. The percentage of patients in the Phase III-1 study meeting the criteria for overall

Figure 2. For all populations analyzed, the proportion of overall responders in the AMITIZA group was significantly greater than the proportion in the placebo group.2
The responder was 13.8% in the AMITIZA-treatment group compared to 7.8% of the placebo group. In the Phase III-2 study, 12.1% of patients in the AMITIZA-treatment group were overall responders compared to 5.7% in the placebo group. The difference was statistically significant in both studies 1 and 2 (P<0.05).

One of the Phase III studies also assessed the rebound effect from the withdrawal of AMITIZA 8 mcg twice daily. Following 12 weeks of treatment, withdrawal of AMITIZA did not result in a rebound effect.2

Patients taking AMITIZA may experience nausea. Concomitant administration of food with AMITIZA may reduce the occurrence of nausea.3 AMITIZA should not be prescribed to patients who have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment with AMITIZA. Patients taking AMITIZA may experience dyspnea within 1 hour of the first dose. This symptom generally resolves within 3 hours, but may recur with repeat dosing. Some patients have discontinued therapy because of dyspnea. Patients on treatment with AMITIZA who experience severe nausea, diarrhea, or dyspnea should inform their healthcare provider.

In the clinical trials for IBS-C, AMITIZA was generally well tolerated. Table 1 notes the adverse events that occurred in ≥1% of patients who were treated with AMITIZA 8 mcg twice daily and that occurred more frequently with AMITIZA than with placebo. These data are compiled from patients enrolled in the Phase II dose-finding study as well as the two Phase III studies: 1011 patients with IBS-C treated with AMITIZA 8 mcg twice daily for up to 12 months and 435 patients who received placebo twice daily for up to 16 weeks. These events only included those possibly or probably related to treatment, as assessed by the investigator. The most common adverse events in the AMITIZA 8 mcg twice-daily arm versus placebo were nausea (8% vs 4%), diarrhea (7% vs 4%), and abdominal pain (5% vs 5%).

In the two 12-week studies, 4.7% of patients taking AMITIZA (n=832) discontinued treatment due to an adverse event compared with 6% of patients taking placebo (n=435).18 In a 36-week open-label safety study, adverse events reported were similar to those in Phase III controlled studies. In this study, 4.8% of patients taking AMITIZA (n=520) discontinued treatment due to an adverse event.

### Other Pharmacologic Agents for IBS-C

One other agent has been approved by the FDA for treatment of IBS-C. Zelnorm® (tegaserod) is a 5-HT4 (serotonin) agonist that was demonstrated to be more effective than placebo in relieving global IBS symptoms in female IBS-C patients. Due to postmarketing safety concerns, however, Zelnorm was withdrawn from the market in 2007 and is now available only for emergency use through the FDA.20

### Emerging Agents for IBS-C

There are 2 investigational drugs currently in clinical trials for treatment of IBS-C. Linaclotide is a guanylate cyclase type C agonist in Phase III trials for treatment of IBS-C and CC.21 Pumosetrag, previously known as DPP733, is a partial 5-HT3 agonist and is currently being evaluated for treatment of IBS-C in Phase IIb trials.22

### Table 1. Percentage of Patients Experiencing Adverse Reactions in AMITIZA Phase II/III IBS-C Trials

<table>
<thead>
<tr>
<th>Incidence of Adverse Reactions ≥1%</th>
<th>AMITIZA 8 mcg Twice Daily n=1011 through 1 year*</th>
<th>Placebo n=435 up to 16 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>3%</td>
<td>2%</td>
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* 12- to 16-week double-blind studies and a 36-week open-label study.
Conclusion

Management of IBS-C has often been suboptimal because of a poor understanding of its etiology and pathophysiology, underdiagnosis of the condition, and a lack of widely available treatments with indications specific to IBS-C. In addition to the benefits that may be achieved through better understanding and awareness of this condition, improvement in the clinician–patient dialogue regarding symptoms and their impact on patients’ daily lives will enhance management. Both clinicians and patients need to recognize the variable symptoms of IBS-C and develop a collaborative relationship that emphasizes empathy, full disclosure from both parties, establishment of realistic treatment plans, and appropriate follow-up care for better management of symptoms.

Currently, AMITIZA is the only widely available FDA-approved option for management of IBS-C in adult women. Clinical evidence from controlled Phase III trials demonstrates that AMITIZA, at a dose of 8 mcg twice daily, is more effective than placebo in this patient population. In a recent evidence-based, systematic review on the management of IBS conducted by the American College of Gastroenterology, AMITIZA received a grade 1B rating, which is a strong recommendation with moderate evidence. Development of new therapeutic agents may increase the number of therapeutic options for patients with IBS-C in the future.

References

Indication

AMITIZA® (lubiprostone) is indicated for the treatment of Irritable Bowel Syndrome With Constipation (8 mcg twice daily) in women ≥18 years old.

Important Safety Information

• AMITIZA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction. Patients with symptoms suggestive of mechanical gastrointestinal obstruction should be thoroughly evaluated by the treating healthcare provider to confirm the absence of such an obstruction prior to initiating AMITIZA treatment.

• The safety of AMITIZA in pregnancy has not been evaluated in humans. AMITIZA should be used during pregnancy only if the benefit justifies the potential risk to the fetus. Women who could become pregnant should have a negative pregnancy test prior to beginning therapy with AMITIZA and should be capable of complying with effective contraceptive measures.

• Patients taking AMITIZA may experience nausea. If this occurs, concomitant administration of food with AMITIZA may reduce symptoms of nausea. Patients who experience severe nausea should inform their healthcare provider.

• AMITIZA should not be prescribed to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment and inform their healthcare provider if the diarrhea becomes severe.

• Patients taking AMITIZA may experience dyspnea within an hour of first dose. This symptom generally resolves within three hours, but may recur with repeat dosing. Patients who experience dyspnea should inform their healthcare provider. Some patients have discontinued therapy because of dyspnea.

• In clinical trials of AMITIZA (8 mcg twice daily vs placebo; N=1,011 vs N=435) in patients with Irritable Bowel Syndrome with Constipation, the most common adverse reactions (incidence >4%) were nausea (8% vs 4%), diarrhea (7% vs 4%), and abdominal pain (5% vs 5%).

Please see attached complete Prescribing Information.

AMITIZA is a registered trademark of Sucampo Pharmaceuticals, Inc.

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Author Disclosure

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